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EXAMINER
PARAS JR, PETER

ART UNIT	PAPER NUMBER
1632	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/472,558	Applicant(s) BAHRAMIAN ET AL.	
	Examiner Peter Paras	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11,13-18,22-25,28-49,51 and 53-56* is/are pending in the application.

4a) Of the above claim(s) *28-49,51 and 53-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,13-18 and 22-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/07/01 has been entered.

Claims 1-10, 12, 19-21, 26-27, 50 and 52 have been cancelled. Claims 11, 17-18, 22 and 24 have been amended. Claims 11, 13-18, 22-25, 28-49, 51, and 53-56 are pending and are under current consideration.

Election/Restrictions

Claims 28-49, 51 and 53-56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 5.

Claim Objections

Claim 17 is objected to because of the following informalities: the term "two portion" in line 5 should be plural. Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The previous rejection of claims 11-27, 50 and 52 is withdrawn under 35 U.S.C. 112, first paragraph.

Applicant's arguments with respect to the previous rejection are moot, as the rejection has been withdrawn.

Applicant's amendments to the claims have necessitated the following new grounds of rejection under 35 U.S.C. 112, first paragraph:

Claims 11, 13-18 and 22-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of muting expression of a α1(I) procollagen in cultured rodent fibroblasts, comprising introducing a plasmid containing a portion of the α1(I) procollagen nucleotide sequence that ranges from –222 to +585, wherein the plasmid is transiently transfected into the rodent fibroblasts and the nucleotide sequence of endogenous α1(I) procollagen is not disrupted, does not reasonably provide enablement for the claimed method comprising any other embodiments. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a method for muting expression of an endogenous gene in a cultured population of animal cells, comprising identifying a muting nucleic

acid composition having a sequence that is homologous to a sequence in the endogenous gene, the nucleic acid sequence being double-stranded or non-complementary with respect to mRNA associated with the endogenous gene, and wherein the nucleic acid sequence is DNA, RNA or a nucleic acid analog, and delivering the muting nucleic acid sequence into the population of cells under conditions devoid of a selection for integration of the nucleic acid sequence into a chromosomal site so that expression of the endogenous gene in the population as a whole is inhibited even though such gene's sequence is not therein disrupted, and wherein the nucleic acid sequence is inserted into a vector that is a plasmid, a recombinant virus, a phagemid, or an attenuated bacterium.

The specification has taught that expression of endogenous α1(I) procollagen gene can be muted in cultured rodent cells by introducing into said cells a vector comprising the entire DNA sequence of the α1(I) procollagen gene, or a portion of the DNA sequence of the α1(I) procollagen gene that includes part of the 5'untranscribed region, part of the coding region, and intronic sequences. See the working examples on pages 21-28 of the specification. Although the specification has recited that the full length α1(I) procollagen gene can mute expression of endogenous sequence, the specification has also pointed out that not all regions of the full length α1(I) procollagen gene contribute to muting. The specification goes on to discuss the effects of different portions of the α1(I) procollagen gene with respect to muting and has suggested that sequences consisting of regions downstream of +585 and that regions upstream of – 222 do not contribute to the muting effect. See pages 28 and 26-27 of the specification,

respectively. The specification has also taught that the muting effect of the α1(I) procollagen gene is not the result of transfection related stress by providing a control that was subject to transfection conditions but did not comprise any exogenous nucleotide sequences; said control did not show a change in endogenous α1(I) procollagen gene expression levels. See working example 8 on pages 24-25 of the specification. Additionally, the specification has provided a mock transfection condition comprising a non-collagen nucleotide sequence, which did not effect levels of endogenous α1(I) procollagen expression.

The specification however, has not taught how to mute expression of the endogenous α1(I) procollagen gene by introducing, into cultured animal cells, a ribonucleic acid sequence or a nucleic acid analog that is homologous to the endogenous α1(I) procollagen gene. The specification has not taught the skilled artisan how to select portions of the α1(I) procollagen transcript or a nucleic acid analog, which would mute expression of the endogenous nucleic acid sequence and has not provided any working examples that correlate use of RNA molecules or nucleic acid analogs with muting expression of any endogenous gene in cultured cells. Furthermore, the specification has not provided any working examples that demonstrate muting of any nucleic acid sequences other than the α1(I) procollagen gene. There is no teaching provided by the instant specification that would suggest whether the muting effect is general, so that it could be applicable to any other gene, or whether the muting effect is only specific to α1(I) procollagen as the mechanism for the muting effect has not been disclosed. In the absence of any relevant teachings with respect to the mechanism of

muting the skilled artisan cannot predict how to achieve muting of other genes. As such guidance is lacking in the instant specification that teaches the skilled artisan how to construct and use other muting nucleic acid sequences. Finally, the instant specification has not taught how to use attenuated bacteria as a vector for introducing a muting nucleic sequence into cultured cells to mute expression of an endogenous nucleic acid sequence.

First, as the mechanism by which muting of expression of an endogenous gene has not been elucidated by the instant specification, the skilled artisan is left to speculate how the invention actually works. The mechanism by which a process occurs does not need to be known for patentability. However, the skilled artisan can raise issues of unpredictability when contemplating the mechanism by which a process occurs, particularly when the claims embrace genes other than that examined by Applicants. The specification asserts that the muting effect is a general phenomenon that can be applied to other genes. However, the working examples provided by the instant specification, on pages 21-28, would appear to suggest the muting effect is not a general phenomenon but rather a sequence specific effect observed with respect to the α1(I) procollagen gene sequence. Support for this interpretation is found in the instant specification, which teaches that α1(I) procollagen sequences upstream of –222 and downstream of +585 do not contribute to muting of α1(I) procollagen. Furthermore, the instant specification has not taught which specific α1(I) procollagen sequences within the region from –222 to +585 are responsible for muting. Without knowledge of the specific sequence(s) responsible for muting, the skilled artisan is not able to predict

which nucleotide sequences from other genes can be used for muting expression. Even more, it not clear what type of molecule is responsible for muting as the mechanism of such has not been disclosed by the instant specification. Based on the teachings of the specification and the claims as written, the skilled artisan could interpret the muting effect to be related to the DNA sequence of the exogenous collagen sequences, RNA transcribed from the exogenous collagen sequences, protein produced from the exogenous collagen sequences, or an effect of transfecting exogenous collagen nucleotide sequences into rodent cells. However, the skilled artisan would need some knowledge or guidance to that end to know how to select and use sequences from other genes for muting. Such guidance is lacking from the instant specification. It would have required undue experimentation for the skilled artisan to practice the invention as claimed in view of the lack of guidance provided by the specification for selecting nucleotide sequences that result in muting.

Next, the use of ribonucleic acid sequences for muting expression of an endogenous nucleic acid sequence in cultured cells is unpredictable and appears to be an inoperable embodiment that lacks support in the instant specification. There are no teachings, guidance, or working examples provided by the instant specification that teach the skilled artisan how to use double-stranded RNA or single stranded RNA to mute the expression of an endogenous gene in a cultured animal cell. In particular, the fate of the RNA molecule introduced into a cultured cell is unclear. It is well known in the art that RNA, particularly double-stranded, is rapidly degraded in a cell by RNAses.

In this case the specification has failed to provide guidance or relevant teachings, which suggest how and where muting of an endogenous gene occurs. As such it is unpredictable if an exogenous RNA molecule is stable when introduced into a cell. For example, if muting occurs in the nucleus, how is an exogenous RNA molecule, when introduced into a cultured cell, transported into the nucleus; it is not clear if such an RNA molecule can even survive the cellular protection mechanisms designed to degrade foreign RNA molecules. Furthermore, if the muting nucleic acid is a single-stranded RNA molecule it is not clear how muting can occur, particularly because the claims require that single-stranded molecules are non-complementary to mRNA, meaning that any exogenous muting single-stranded RNA molecule must have the same sequence as the endogenous mRNA molecule. There is no evidence provided by the specification or the prior art that suggests that mRNA molecules of the same sequence (one being exogenous and one being endogenous) can reduce their own expression levels.

Even more, with regard to claim 23, if the muting nucleic acid molecule is an RNA molecule it cannot comprise a 3' portion of the gene that is not transcribed. Such a claim embodiment is inoperable because it cannot exist since by definition an RNA molecule is a transcript of a gene's coding sequences. In light of such it is unclear how an RNA molecule, when introduced into a cell, can mute expression of any endogenous gene. Given the lack of guidance provided by the instant specification, it would have required undue experimentation to use an RNA molecule to mute expression of a gene.

Furthermore, the specification has not taught how to insert an RNA molecule into a DNA vector, the vector being a plasmid, phagemid, virus, or attenuated bacterium. Such methodology is not routine in the art and is not supported by the teachings or working examples of the instant specification. It is unpredictable, for example, if a single-stranded RNA molecule can be inserted into a double-stranded DNA vector. Given the lack of guidance provided by the instant specification, it would have required undue experimentation to insert an RNA molecule into a vector for use in the claimed method.

Finally, claim 25 recites the embodiment of using attenuated bacteria for delivering the muting nucleic acid into a cell such that the expression of an endogenous gene is inhibited in a population of cultured cells as a whole. The state of the art suggests that use of attenuated bacteria as a means of gene transfer is inefficient, undeveloped, and unpredictable with respect to delivery of a muting nucleic acid molecule that may inhibit expression of an endogenous gene in a population of cultured cells as a whole.

For bacteria to function as DNA delivery systems into mammalian cells, the bacteria must first enter the cell and then escape from the vacuole to the cytosol. Movement from the vacuole to the cytosol is unpredictable because in many instances the bacteria are lysed by the host cell's defense system and any plasmids carried by the bacteria are degraded preventing expression of heterologous nucleotide sequences. At best it would appear that only a few cells, if any may be transformed with plasmid DNA carried by a bacterial vehicle as Grillot-Courvalin (Nature Biotechnology, 1998, 16: 862-

866) suggest that "direct introduction of DNA from bacteria to mammalian cells has been reported in very few instances". See page 865, starting with the first line of the discussion. Grillot-Courvalin support such observations by reporting that "factors such as entry route may have an effect" on DNA delivery. Grillot-Courvalin go on to report that a mouse dendritic cell line, which can internalize bacteria via micropinocytosis, did not express incoming DNA at 24 hours post-transfer. Grillot-Courvalin suggest that this failure could reflect rapid degradation of the invading bacteria by this cell type. It would appear that use of bacteria as DNA delivery vehicles is not very efficient in other cell lines as well as Grillot-Courvalin have reported that *E.coli* carrying a nucleotide sequence encoding the green fluorescent protein are only able to transform 0.3-1% of a transfected macrophage cell line. See the paragraph bridging pages 864-865. These observations are corroborated by Dietrich et al (Nature Biotechnology, 1998, 16: 181-185) who report that only about 0.03% of macrophages infected with a mutated form of *Listeria monocytogenes* express a green fluorescent protein reporter gene. See page 183, column 2. Dietrich et al also suggest that expression of a heterologous nucleotide sequence is not stable over time by observing a gradual loss of fluorescence over time. See page 183 at the bottom of column 2. Dietrich report that the low efficiency of expression of GFP as compared to the number of macrophages infected may be due to the fact that "only some of the attenuated bacteria infecting the host cells survive the antimicrobial milieu inside the phagosome and are able to escape into the host cell cytosol, whereas the others are totally digested, including the plasmid DNA and that not all listeriae being taken up reach the host cell cytosol as an intact viable entity, but the

plasmid DNA is still released into this compartment. See page 184 at the top of column 2. Given the lack of guidance provided by the instant specification it would have required undue experimentation to use an attenuated bacterium to deliver a muting nucleic acid molecule to cultured cells such that expression of an endogenous gene is inhibited in the cell population as a whole.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for muting of any gene, the lack of direction or guidance provided by the specification for the muting of any gene using an RNA molecule or a nucleic acid analog as a muting nucleic acid, the lack of direction or guidance provided by the specification for the insertion of an RNA molecule into a DNA vector, the absence of working examples for the demonstration or correlation to the muting of any gene using an RNA molecule or a nucleic acid analog as a muting nucleic acid, the unpredictable state of the art with respect to stability of exogenous RNA in a cell, the undeveloped state of the art with respect to use of an attenuated bacterium as a vector for delivering a muting nucleic acid molecule to cultured cells, wherein the muting nucleic acid molecule inhibits expression of an endogenous gene in the cell population as a whole, and the breadth of the claim drawn to methods of muting expression of any gene in a cultured cell, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The previous rejections of claims 1-27, 50 and 52 under 35 U.S.C. 112, second paragraph is withdrawn.

Applicant's arguments with respect to the previous rejection are moot, as the rejection has been withdrawn.

The following are new grounds of rejection under 35 U.S.C. 112, second paragraph:

Claims 17-18 and 22-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 is indefinite as written because the claim recites the following phrase "a transcribed coding portion including introns". The phrase is indefinite because introns are not coding regions of a nucleotide sequence. It is unclear how a coding region of nucleotide sequence can include introns. Claims 18 and 22-23 depend from claim 17.

Claim 23 is indefinite as written because the claim recites that a muting nucleic acid comprises a sequence that is homologous to an endogenous 3' sequence of a gene, wherein the endogenous sequence includes an untranscribed portion and a portion that overlaps the 3' end of the coding portion. It is unclear, how the muting nucleic acid, if it is an RNA molecule, can comprise an untranscribed portion of an

endogenous gene. RNA molecules by definition are transcripts of coding regions of a gene.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The previous rejection of claims 1-17, 22-24, 50 under 35 U.S.C. 102(b) as being anticipated by Capecchi is withdrawn.

Applicant's arguments with respect to the previous rejection are moot, as the rejection has been withdrawn.

The following new grounds of rejection under 35 U.S.C. 102(b) have been necessitated by Applicant's amendments to the claims:

Claims 11, 13-18, 22 and 24 as amended or originally filed are rejected under 35 U.S.C. 102(b) as being anticipated by Guimaraes et al (1996, PNAS, 93: 15086-15091).

The claims are directed to a method for muting expression of an endogenous gene in a cultured population of animal cells, comprising identifying a muting nucleic acid composition having a sequence that is homologous to a sequence in the

endogenous gene, the nucleic acid sequence being double-stranded or non-complementary with respect to mRNA associated with the endogenous gene, and wherein the nucleic acid sequence is DNA, RNA or a nucleic acid analog, and delivering the muting nucleic acid sequence into the population of cells under conditions devoid of a selection for integration of the nucleic acid sequence into a chromosomal site so that expression of the endogenous gene in the population as a whole is inhibited even though such gene's sequence is not therein disrupted, and wherein the nucleic acid sequence is inserted into a vector that is a plasmid, a recombinant virus, or a phagemid.

Guimaraes et al teach the isolation and cloning of Sps2 homologs from mice and humans. See Materials and Methods on pages 15086-15087. Guimaraes et al further teach that Sps2 homologs are found in different species. See Fig. 2 on page 15089. Guimaraes et al teach the transfection of a plasmid comprising Sps2 cDNA into COS-7 cells, without disrupting the endogenous Sps2 sequence. See Materials and Methods on page 15087, and also page 15090 in column 1. Also, the Sps2 cDNA sequence of Guimaraes is homologous to 5' and 3' regions as well as a portion that overlaps adjacent ends of at least two portions of the endogenous Sps2 gene. If the muting method is general in effect to all genes as asserted in the specification then it is inherent that expression of the endogenous Sps2 gene in COS-7 cells must be inhibited. The claim only requires that the muting nucleic acid be homologous to a sequence in the endogenous gene, wherein the muting nucleic acid sequence is double-stranded and that the muting nucleic acid sequence is delivered into a population of cultured cells, wherein the muting nucleic acid is not selected for integration into the host DNA. The

teachings of Guimaraes certainly meet all of these claim requirements as the Sps2 cDNA is homologous to the endogenous Sps2 sequence, the Sps2 cDNA is inserted into a plasmid and is double-stranded, and the Sps2 plasmid is transfected into COS-7 cells and does not integrate into the COS-7 genome. If Applicant's assertion is correct, then it is inherent that the exogenous Sps2 nucleotide sequence inhibited the expression of endogenous Sps2 nucleotide sequences as all of the claim requirements for the nucleic acid sequence, cells, and vector have been anticipated by Guimaraes et al.

Thus, the teachings of Guimaraes et al anticipate all of the instant claim limitations.

Claims 11, 13-18, and 24 as amended or originally filed are rejected under 35 U.S.C. 102(b) as being anticipated by Gambarotta et al (1996, Oncogene, 13: 1911-1917).

The claims are directed to a method for muting expression of an endogenous gene in a cultured population of animal cells, comprising identifying a muting nucleic acid composition having a sequence that is homologous to a sequence in the endogenous gene, the nucleic acid sequence being double-stranded or non-complementary with respect to mRNA associated with the endogenous gene, and wherein the nucleic acid sequence is DNA, RNA or a nucleic acid analog, and delivering the muting nucleic acid sequence into the population of cells under conditions devoid of a selection for integration of the nucleic acid sequence into a chromosomal site so that

expression of the endogenous gene in the population as a whole is inhibited even though such gene's sequence is not therein disrupted, and wherein the nucleic acid sequence is inserted into a vector that is a plasmid, a recombinant virus, or a phagemid.

Gambarotta et al teach a method of reducing the expression of the Met gene by introducing a plasmid, into cultured mouse and human cells, comprising a nucleic acid sequence comprising ETS1 binding sites, which are naturally found in the Met promoter region [the promoter region is a 5' untranscribed region of the Met gene], wherein the nucleic acid sequence acts as a "decoy" to inhibit binding of ETS1 to native sites in the Met promoter, and wherein expression of Met is dramatically reduced. See the abstract and throughout the entire document. The method of Gambarotta does not require exogenous DNA integration or disruption of an endogenous nucleotide sequence.

Thus, the teachings of Gamboratta et al anticipate all of the instant claim limitations.

Claims 11, 13-18, 22, and 24 as amended or originally filed are rejected under 35 U.S.C. 102(b) as being anticipated by Rippe (1989, Molecular and Cellular Biology, 9(5): 2224-2227; IDS-#AL).

The claims are directed to a method for muting expression of an endogenous gene in a cultured population of animal cells, comprising identifying a muting nucleic acid composition having a sequence that is homologous to a sequence in the endogenous gene, the nucleic acid sequence being double-stranded or non-complementary with respect to mRNA associated with the endogenous gene, and

wherein the nucleic acid sequence is DNA, RNA or a nucleic acid analog, and delivering the muting nucleic acid sequence into the population of cells under conditions devoid of a selection for integration of the nucleic acid sequence into a chromosomal site so that expression of the endogenous gene in the population as a whole is inhibited even though such gene's sequence is not therein disrupted, and wherein the nucleic acid sequence is inserted into a vector that is a plasmid, a recombinant virus, or a phagemid.

Rippe et al teach a method of transfecting mouse cells with a plasmid comprising a nucleotide sequence that comprises part of the mouse alpha 1 type 1 collagen gene promoter and part of the first exon [these sequences correspond to the 5'untranscribed region and the 5' coding region are homologous to the endogenous mouse alpha 1 type 1 collagen gene]. See page 2224 and throughout the entire document. The method of Rippe et al does not require integration into the mouse genome or disruption of the endogenous collagen gene. If the muting method is general in effect to all genes as asserted in the specification then it is inherent that expression of the endogenous alpha 1 type 1 collagen gene in mouse cells must be inhibited. The claim only requires that the muting nucleic acid be homologous to a sequence in the endogenous gene, wherein the muting nucleic acid sequence is double-stranded and that the muting nucleic acid sequence is delivered into a population of cultured cells, wherein the muting nucleic acid is not selected for integration into the host DNA. The teachings of Rippe certainly meet all of these claim requirements as the collagen sequence used are homologous to the endogenous alpha 1 type 1 collagen gene sequence, the collagen sequences are inserted into a plasmid and are double-stranded, and such plasmid is transfected into

NIH 3T3 cells and does not integrate into the 3T3 genome. If Applicant's assertion is correct, then it is inherent that the exogenous collagen nucleotide sequence inhibited the expression of endogenous alpha 1 type 1 collagen nucleotide sequences as all of the claim requirements for the nucleic acid sequence, cells, and vector have been anticipated by Rippe et al.

Thus, the teachings of Rippe anticipate all of the instant claim limitations.

Claims 11, 13-17, and 22-23 as amended or originally filed are rejected under 35 U.S.C. 102(b) as being anticipated by Slack et al (1992, Molecular and Cellular Biology, p4714-4723; IDS-# AX).

The claims are directed to a method for muting expression of an endogenous gene in a cultured population of animal cells, comprising identifying a muting nucleic acid composition having a sequence that is homologous to a sequence in the endogenous gene, the nucleic acid sequence being double-stranded or non-complementary with respect to mRNA associated with the endogenous gene, and wherein the nucleic acid sequence is DNA, RNA or a nucleic acid analog, and delivering the muting nucleic acid sequence into the population of cells under conditions devoid of a selection for integration of the nucleic acid sequence into a chromosomal site so that expression of the endogenous gene in the population as a whole is inhibited even though such gene's sequence is not therein disrupted, and wherein the nucleic acid sequence is inserted into a vector that is a plasmid, a recombinant virus, or a phagemid.

Slack et al teach a method of transfecting rat cells with a plasmid comprising a nucleotide sequence that comprises a portion of the 3' coding and 3' untranslated region of the human alpha 1 (I) collagen gene, which is homologous to the endogenous collagen nucleotide sequence. See Materials and Methods on page 4715 and page 4719 2nd column. The method of Slack et al does not require integration into the mouse genome or disruption of the endogenous collagen gene. If the muting method is general in effect to all genes as asserted in the specification then it is inherent that expression of the endogenous alpha 1 type 1 collagen gene in mouse cells must be inhibited. The claim only requires that the muting nucleic acid be homologous to a sequence in the endogenous gene, wherein the muting nucleic acid sequence is double-stranded and that the muting nucleic acid sequence is delivered into a population of cultured cells, wherein the muting nucleic acid is not selected for integration into the host DNA. The teachings of Slack certainly meet all of these claim requirements as the collagen sequence used are homologous to the endogenous alpha 1 type 1 collagen gene sequence, the collagen sequences are inserted into a plasmid and are double-stranded, and such plasmid is transfected into rat cells and does not integrate into the rat genome. If Applicant's assertion is correct, then it is inherent that the exogenous collagen nucleotide sequence inhibited the expression of endogenous alpha 1 type 1 collagen nucleotide sequences as all of the claim requirements for the nucleic acid sequence, cells, and vector have been anticipated by Slack et al.

Thus, the teachings of Slack et al anticipate all of the instant claim limitations.

Claims 11, 13-18, and 24-25 as amended or originally filed are rejected under 35 U.S.C. 102(b) as being anticipated by Chan et al (1991, Molecular and Cellular Biology, 11(1): 47-54; IDS-#AR).

The claims are directed to a method for muting expression of an endogenous gene in a cultured population of animal cells, comprising identifying a muting nucleic acid composition having a sequence that is homologous to a sequence in the endogenous gene, the nucleic acid sequence being double-stranded or non-complementary with respect to mRNA associated with the endogenous gene, and wherein the nucleic acid sequence is DNA, RNA or a nucleic acid analog, and delivering the muting nucleic acid sequence into the population of cells under conditions devoid of a selection for integration of the nucleic acid sequence into a chromosomal site so that expression of the endogenous gene in the population as a whole is inhibited even though such gene's sequence is not therein disrupted, and wherein the nucleic acid sequence is inserted into a vector that is a plasmid, a recombinant virus, or a phagemid.

Chan et al teach a method of transfecting rat cells with a plasmid comprising a nucleotide sequence that comprises a Moloney murine leukemia provirus flanked by a 5' untranscribed region and a portion of the 5' coding region of the mouse alpha 1type I collagen gene. See page 47, and Materials and Methods on pages 48-49, as well as figure 1 on page 48. The method of Chan et al does not require integration into the mouse genome or disruption of the endogenous collagen gene. If the muting method is general in effect to all genes as asserted in the specification then it is inherent that expression of the endogenous alpha 1 type 1 collagen gene in mouse cells must be

inhibited. The claim only requires that the muting nucleic acid be homologous to a sequence in the endogenous gene, wherein the muting nucleic acid sequence is double-stranded and that the muting nucleic acid sequence is delivered into a population of cultured cells, wherein the muting nucleic acid is not selected for integration into the host DNA. The teachings of Chan certainly meet all of these claim requirements as the collagen sequence used are homologous to the endogenous alpha 1 type 1 collagen gene sequence, the collagen sequences are inserted into a plasmid and are double-stranded, and such plasmid is transfected into rat cells and does not integrate into the rat genome. If Applicant's assertion is correct, then it is inherent that the exogenous collagen nucleotide sequence inhibited the expression of endogenous alpha 1 type 1 collagen nucleotide sequences as all of the claim requirements for the nucleic acid sequence, cells, and vector have been anticipated by Chan et al.

Thus, the teachings of Chan et al anticipate all of the instant claim limitations.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The previous rejection of claims 1, 8-10, 12, 17-21, 25-27, and 52 under 35 U.S.C. 103(a) as being unpatentable over Capecchi et al is withdrawn.

Applicant's arguments with respect to the previous rejection are moot, as the rejection has been withdrawn.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached at 703-305-4051. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703) 308-4242 and (703) 305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to Patsy Zimmerman whose telephone number is (703) 305-2758.

Peter Paras, Jr.

Art Unit 1632

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER